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Physiological interaction of SARS-CoV-2 binding to the ACE-2 receptor

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***Abstract*---**For a better knowledge of how viruses enter cells, the associations that are created between the viral glycoproteins and associated human receptors must be studied. The spike glycoprotein (S-glycoprotein) of the new coronavirus SARS-CoV-2 mediates entrance into host cells, and the cellular receptor angiotensin-converting enzyme 2 (ACE-2) has been discovered.The goal of our research was to evaluate the physiological interactions between the SARSCoV-2 and the human cell receptor ACE-2.Modifications were

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discovered in the S1 monomer of the receptor-binding domain of spikes using an in silico analysis. The observed modifications have a considerable impact on the interlinkage between the SARS-CoV-2 spike and ACE-2. According to the research outcome, the SARS-Cov-2 spikes proteinhas a strong attraction for the human ACE-2 receptor than the Bat-CoV spikes does. Further, the presence of two loops throughout the SARS-CoV-2 receptor binding domain (RBD) may facilitate binding to the ACE-2 (receptor)throughenhancing the quantity of atoms implicated. The reason SARS-CoV-2 binds to substrates with higher binding energies than SARS-CoV may be due to longer capping loops and changed amino acids.

***Keywords*---**Coronavirus, Angiotensin-converting enzyme 2, Physiological interaction, Spikes protein.

Introduction

In Wuhan, China, in December 2019, a deadly atypical pneumonia outbreak that was later named coronavirus disease-19 was revealed to be brought on by a novel coronavirus (CoV). It was found that the new SARS-CoV-2, which triggered the SARS pandemic in 2002, had traits with the SARS-CoVthat caused that epidemic.

The subsequent COVID-19 pandemic has developed into a significant scourge.

The SARS-CoV-2 genome is 94% equal to the BATCoV and 81% identical to the SARS-CoVgenome[1-3].

The family Coronaviridae and the genus-coronavirus, which have all been connected to important epidemic outbreaks, include SARS-CoV-2 andwell-known recombinant SARS-CoV. The positive-sense single-strand RNA of these viruses is roughly 34 kilobases long and is encapsulated [4]. The four main functional proteins present in virions are the spikes, cell wall, a protein coat, and nucleo-capsid [5]. The receptor's host specificity and intracellular adhesion depend on the Spikes, which protrudes from the virion's outer membrane [6]. Angiotensin-converting enzyme 2 (ACE-2) is known to bind with the SARS-CoV and SARS-CoV-2via spikes attach to protein [7,8]. However, it appears that ACE-2 serves as the primary basic ligand for both SARS-CoV and SARS-CoV-2 [9].

The interaction between the viral protein and its receptor on the cellular membranes is a critical step in the reproduction phase of the virus [10,11].

Additionally, the effectiveness of an infectious disease is significantly impacted by this mechanism. Many physical factors affect how proteins interact with one another. These components are influenced by the types of molecules and physiological interactions that take place between the receptor and ligand. The occurrence of residue that leads to an operationally preferable contact (lower free energy) may therefore encourage interaction kinematics and ultimately lead to the fusion process [12,13]. Therefore, the goal of our research was to evaluate the

physiological interactions among the SARS-CoV-2and ACE-2 receptor cell of human.

Methods

Each sequence being studied received a distinct GenBank retrieval. Information from the protein data library was used to develop the spikes-related proteins model of the amino acid sequence of SARS-CoV-2. The virus Spikes from Bat-CoV and SARS-CoV-2were modeled using Deep-PdbViewer 4.03 program and the SWISS-MODEL. The ideal models for the SARS-CoV-2 Spikesbesides Bat-CoV were made by means of the crystal structures of PDB code 6ACD and SARS-CoV Spikes, respectively. These models underwent additional protein structural tuning. After the hydrogen atoms were added, the energy was improved by using fractional ions. Then, energy was reduced by enhancing the comparative locations of protein and water molecules and placing constraints on the protein chain to preserve global packing. Molecular dynamics (MD) simulations were performed on the collected devices using NAMD software. The created structures illustrated the least-energy framework from the MD simulation.

The crystal structures of the SARS-CoV spikes (Portien Data Bank number 6-ACK) and ACE-2 were retrieved from the Protein Sequences Bank (Protein data bank number 1R-42). Also looked at was the SARS-CoV-2spikes' homologous framework. The aforementioned description indicates that the protein was prepared. Finally, the link between the virus spikes and ACE-2 receptor was created using molecular docking, adsorption configurations, and intensity estimates. There were two stages to this process. The ACE-2 receptor and the Spikeswere first docked blindly using the Z-dock software. The resulting docking data was then analyzed and evaluated using the PRODIGY app's features. The results were then categorized and assessed while accounting for the main linking residues and relative intensities in each compound.

Results

The SARS-CoVas well as a phylogenetic analysis of the Spikessequences of Bat-CoVs, including SARS-CoV-2are revealed in figure 1. The outcomes areconsistent with earlier research suggesting that SARS-CoV-2 originated after a Bat-CoV apart from the overflow that gave rise to SARS-CoV, and that the novel virus' most likely ancestor is a Bat-CoV of the Rhinolophus subsp. SARS-CoV-2plus this Bat-whole CoV's spike share 97.70% of the same sequence (figure 1). The RBD of SARS-CoV and Bat-CoV from Rhinolophussubspp exhibits a variety of peptide losses and modifications when compared to SARS-CoV-2. Even though it resembled the SARS-CoVmuch more, the RBD of the Bat-CoV from Rhinolophussubspp likewise displayed several peptide alterations (figure 2).

Along with the crystalline configuration of the SARS-CoVSpikes, the homology structures of BatCoV (genbank accession code MG772933), BatCoV of Rhinolophus(sinicussubspp) and SARS-CoV-2 associated with the linking affinity domain placement in human ACE-2 were studied. The threevirus-related spikes interact pretty similarly. The coresection of contact with the hypothetical cell receptor homologue, which is made up of 15 residues organized in a β-sheet form,

is enclosed by two capping loops. Surprisingly, a comparison of the SARS-CoV-2 sequences and SARS-CoVrevealed that there is a possibility that the 9 residues in the receptor-related domain shared by both viruses are evolutionarily conserved (69.9% similarity). The discovery of the human ACE-2 receptors has been connected to two crucial residues (487 and 479) in the SARS-CoV. N501 and Q493 are the residues that are equivalent to T487 and N479 in the SARS-CoV-2, respectively. These SARS-CoV-2 alterations could be beneficial for how the virus interacts with its receptor. These modifications are encouraged by the environment of the ACE-2 receptor to yield a large amount of electrical alleviating connections (table 1). The two capping loops in the binding domain are also probable to make a stronger connection with the cell surface receptor, as was already mentioned. According to the findings shown above, the aforementioned capping loops improve the electrical connections between the Spikesand the cell receptor. S432, N473, S472, D463, R426, Y436, T433, and T433 are among the residues in such capping loops in SARS-CoV that communicate with the receptor directly, whereas N487, F486, E484, G485, A475, Q474, V445, and Y473 and Y449 are common residues in SARS-CoV. The counter pairs present in the ACE-2 receptor is exposed in Table 1. Overall, the longer capping loops and improved protein interactions (Figure 3) may be to blame for greater SARS-CoV-2 binding energies (-16.7 Kcal/mol) than SARSCoV (15.1 Kcal/mol). These loops might therefore be essential and an intriguing sign of the hosting receptor virus Spikesalong with punctual alterations (Table 2).

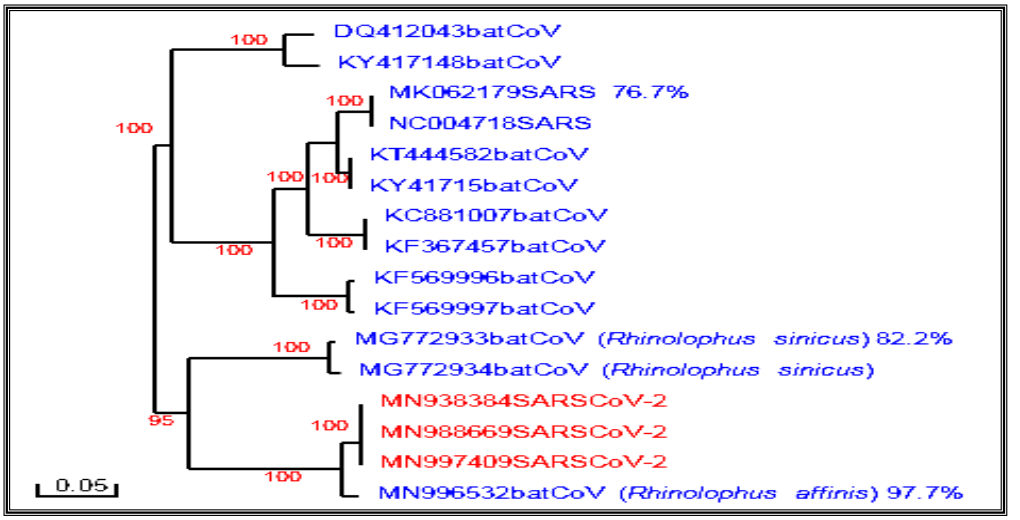

Figure 1: SARS-CoV-2 evolutionary study and also other COV Spikes.

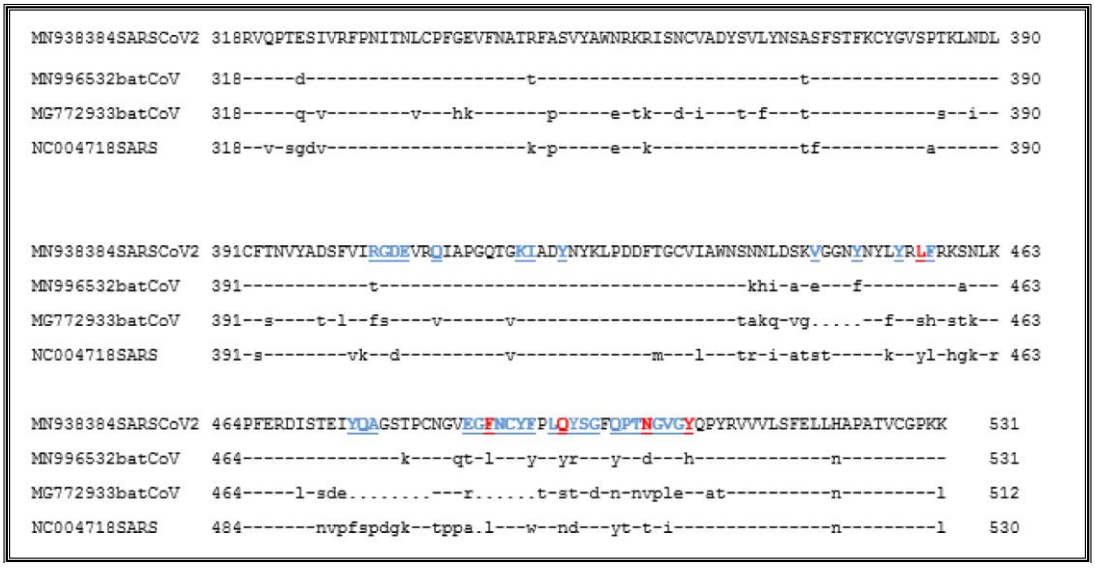

Figure 2: Receptor Attachment Sequencing of the SARS-CoV-2 and certain other similar CoVSpikesdomains.

Table 1: The residues implicated in the association among ACE-2 and the virus spike (SARS)

SARS-CoV-2spikes	***ACE-2***	**SARS-CoV Spikes**	***ACE-2***
F490	Q60, N58	D38	Q492
Y489	E57, E56,N49,A46,L45	Y491	Y83,M89,S19
C487	L46	I489	Q325, Q42
N487	S44,S43,142,Y41	G488	D355, Q325, D38
F486	Y41, F40, L39	T487	K353, L45, H34, G326, G354
G485	L39	T486	K31, K353, L45, G354
E484	D38	T485	G354, G352
A475	D38	Y484	Y41, T27, F28, K353
Q474	D38	F483	E329
Y473	D38	G482	Q42, D38
F456	A36, E35,E37	S432	E329
L455	E35, H34	Y440	S19

Y453	H34, N33	L443	Q24
Y449	N33	D463	D355
V445	F32, k31	K353	Y481
Y421	K31	Y475	T324, T27,Y41
I418	K31	T433	L79
Q409	P28	P462	E35, E329
K417	D30, K31, L29	R426	A25, T27
R408	F28	TY442	Y41, K353
E406	T27	N479	N330, R393
G404	Q24	N473	N330, R357,D355
R403	E23, I21, Q24	Y436	Y41, Y83, T324
D405	A25, Q24, T27, K26		
V503	E329		
G502	L100, Y83		
G504	G352, L351, N330		
N501	,Y83, Q81, M82		
G496	K68		
L492	Q60		
Y495	K68, A65		
T500	A80, L79		
P499	T78, Q76		
S494	A65, N64, N61		

Figure3:CoV spikes and ACE-2 have a certain number of protein-protein interactions

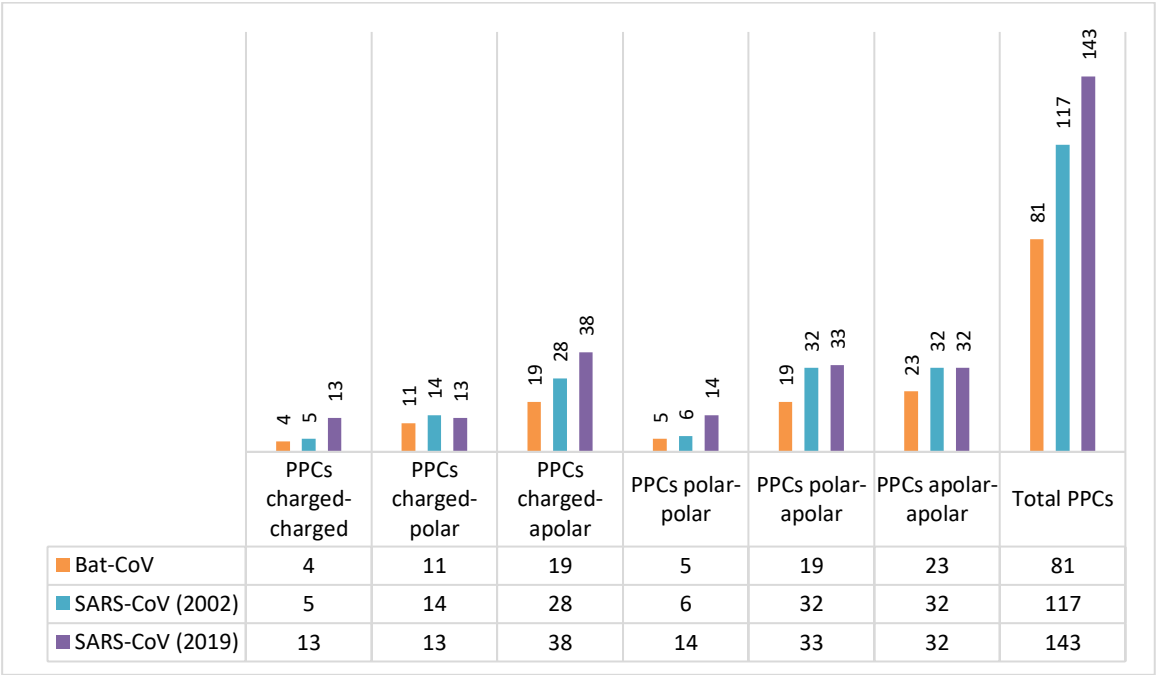

Table2: Parameter estimates for the association among the virus spike and the ACE-2 receptor in terms of binding energy and dissociation constants (Kd)

Virus	**Binding Energy**	**dissociation constants at25^{0}C**
Bat-CoV	-8.2 kcal/mol	$1.0x10^{-4}$
SARS CoV (2002)	-15.1 kcal/mol	$1.2x10^{-12}$
SARS-CoV(2019)	-16.7 kcal/mol	$5.0x10^{-14}$

Discussion

The SARS-CoV-2RBD differs from SARS-CoVand Bat-SARS-CoVs because that it possesses several altered amino acids. Mutations in the Spikescan alter a virus's tropism, adding additional hosts or increasing the pathogenicity of the virus [14].

HIV infection is a prominent illustration of how variations in the envelope proteins may alter the viral tropism. Changing the co-receptor from CCR5 to CXCR4, these changes boost the viral pathogenicity [15].

Surprisingly, our research displayed that these alterations are linked to the receptor's capability to connect with human ACE-2 receptors as well as its ability to increase identification. Two loops that are present throughout the SARS-CoV-2 RBD may make it easier to interact with the ACE-2 (receptor) by emnhancing the

quantity of atoms implicated in the binding process. The longer capping loops and the altered amino acids could be the root of greater SARS-CoV-2 binding energies than SARS-CoV. Advanced affinity levels may be linked to the dynamics of infection and the virus's alleged quick spread. The SARS-CoV-2 that caused SARS has not been fully explained. While this analysis was continuing, another study found a substantial RBD protein homology between RhinolophusaffinisSubspp, pangolin, and SARS-CoV-2 coronavirus isolates [16,17]. In addition, the researchers hypothesize that Pangolin, which shares 97.99% of the virus's binding affinity pattern with humans, could serve as a bridge between bats and humans. Additionally noticeable are the loops in the RBD, and RaTG13's spike structure is strikingly comparable to that of SARS-CoV and SARS-CoV-2. The protein sequence of the receptor binding motif contains five essential amino acids.

The sequence of SARS-CoV-2 differs from the pure viruses from pangolin and Rhinolophusaffinis by 1 and 4 amino acids, respectively, in the amino acids assumed to be essential for the union with ACE-2 [18-20]. As shown in our work, these changes should lead to a slightly less favorable contact affinity between such viruses and ACE-2 thanSARS-CoV-2. As a result, in addition to the amino acid changes, the loops present in the SARS-CoV-2Spikesmay be essential for defining the host receptor sensitivity of the viral Spikes. Overall, fundamental modifications and changes to the viral Spikesresidue composition may improve the kinetics of viral infections and their spread.

Conclusion

It is concluded SARS-CoV-2 and the human cell receptor ACE-2 have an interaction. SARS-CoV-2 pathogenicity is increased by switching from CCR5 to CXCR4 as the co-receptor. These modifications affect the receptor's capacity to interrelatethrough human ACE-2 (receptors) and enhance identification. The presence of two loops throughout the SARS-CoV-2 RBD may facilitate ACE-2 receptor bindingviaenhancing the quantity of atoms implicated. The reason SARS-CoV-2 greater binds to substrates with higher binding energies than SARS-CoVmay be due to longer capping loops and changed amino acids.

References

1. Lauer, S. A., Grantz, K. H., Bi, Q., Jones, F. K., Zheng, Q., Meredith, H. R., ... &Lessler, J. (2020). The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Annals of internal medicine*, *172*(9), 577-582.
2. KamelBoulos, M. N., &Geraghty, E. M. (2020). Geographical tracking and mapping of coronavirus disease COVID-19/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic and associated events around the world: how 21st century GIS technologies are supporting the global fight against outbreaks and epidemics. *International journal of health geographics*, *19*(1), 1-12.
3. Zhou, P., Yang, X. L., Wang, X. G., Hu, B., Zhang, L., Zhang, W., ... & Shi, Z. L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *nature*, *579*(7798), 270-273.

4. Babarinsa, I. A., Okunoye, G. O., &Odukoya, O. (2021). Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infections in pregnancy–An overview. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *263*, 171-175.
5. Schoeman, D., & Fielding, B. C. (2019). Coronavirus envelope protein: current knowledge. *Virology journal*, *16*(1), 1-22.
6. Ortega, J. T., Serrano, M. L., Pujol, F. H., & Rangel, H. R. (2020). Role of changes in SARS-CoV-2 spike protein in the interaction with the human ACE2 receptor: An in silico analysis. *EXCLI journal*, *19*, 410.
7. Chen Y, Guo Y, Pan Y, Zhao ZJ. Structure analysis of the receptor binding of 2019-nCoV. BiochemBiophys Res Commun. 2020;17:S0006-291X(20)30339-9.
8. Wan Y, Shang J, Graham R, Baric RS, Li L. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virol. 2020;epub ahead of print.
9. Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res. 2020;10(176):104742.
10. Satija N, Lal SK. The molecular biology of SARS coronavirus. Ann NY Acad Sci. 2007;1102:26-38.
11. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020; 6:S0092-8674(20)30262-2
12. Chazal, N., &Gerlier, D. (2003). Virus entry, assembly, budding, and membrane rafts. *Microbiology and molecular biology reviews*, *67*(2), 226-237.
13. Ortega, J. T., Serrano, M. L., Pujol, F. H., & Rangel, H. R. (2020). Role of changes in SARS-CoV-2 spike protein in the interaction with the human ACE2 receptor: An in silico analysis. *EXCLI journal*, *19*, 410.
14. Shang J, Wan Y, Liu C, Yount B, Gully K, Yang Y, et al. Structure of mouse coronavirus spike protein complexed with receptor reveals mechanism for viral entry. PLoSPathog. 2020;16(3):e1008392.
15. Mosier DE. How HIV changes its tropism: evolution and adaptation? CurrOpin HIV AIDS. 2009;4:125- 30.
16. Wong MC, JavornikCreegen SJ, Ajami NJ, Petrosino JF. Evidence of recombination in coronaviruses implicating pangolin origins of nCoV-2019. bioRxiv. 2020;
17. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020; 6:S0092-8674(20)30262-2.
18. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of the SARS-CoV-2 by full-length human ACE2. Science. 2020;epub ahead of print.
19. Wiederstein M, Sippl MJ. ProSA-web: interactive web service for the recognition of errors in threedimensional structures of proteins. Nucleic Acids Res. 2007; 35:W407–10.
20. Xue LC, Rodrigues JP, Kastritis PL, Bonvin AM, Vangone A. PRODIGY: a web server for predicting the binding affinity of protein-protein complexes. Bioinformatics. 2016;32:3676-8.